Particulate Air Pollution, Ambulatory Heart Rate Variability, and Cardiac Arrhythmia in Retirement Community Residents with Coronary Artery Disease

Scott M. Bartell, John Longhurst, Thomas Tjoa,
Constantinos Sioutas and Ralph J. Delfino

NIH National Institute of
Environmental Health Sciences

Particulate Air Pollution, Ambulatory Heart Rate Variability, and Cardiac Arrhythmia in Retirement Community Residents with Coronary Artery Disease

Scott M. Bartell[1,2], John Longhurst[3], Thomas Tjoa[2], Constantinos Sioutas[4], and Ralph J. Delfino[2]

[1] Program in Public Health and Department of Statistics, University of California, Irvine, California, USA

[2] Department of Epidemiology, School of Medicine, University of California, Irvine, California, USA

[3] Susan Samueli Center for Integrative Medicine, and Cardiology Division, Department of Medicine, School of Medicine, University of California, Irvine, California, USA

[4] Department of Civil and Environmental Engineering, Viterbi School of Engineering, University of Southern California, Los Angeles, California, USA

Correspondence:

Scott M. Bartell, PhD

Associate Professor

Program in Public Health

2032 Anteater Instruction & Research Building

Irvine, CA 92697-3957

Tele: +1.949.824.5919

Fax: +1.949.824.1343

Email: sbartell@uci.edu

Running title: PM, HRV, and arrhythmia in CAD patients

Competing interests declaration: C.S. receives royalties from SKC Inc. for the air sampling device (Sioutas™ Personal Cascade Impactor Sampler) used in this research. The other authors declare they have no competing financial interests.

Abstract

Background: Decreased heart rate variability has been associated with future cardiac morbidity and mortality, and is often used as a marker of altered cardiac autonomic balance in studies of health effects of airborne particulate matter. Fewer studies have evaluated associations between air pollutants and cardiac arrhythmia.

Objectives: To examine relationships between cardiac arrhythmias, heart rate variability, and exposures to airborne particulate matter.

Methods: We measured heart rate variability and arrhythmia with ambulatory electrocardiograms in a cohort panel study for up to 235 hours among 50 nonsmokers with coronary artery disease age 71 years and older living in four retirement communities in the Los Angeles Air Basin. Exposures included hourly outdoor gases, hourly traffic-related and secondary organic aerosol markers, and daily size-fractionated particle mass. We used repeated measures analyses adjusting for actigraph-derived physical activity and heart rate, temperature, day of week, season, and community location.

Results: Ventricular tachycardia was significantly increased in association with interquartile range increases in markers of traffic-related particles, secondary organic carbon, and ozone. Few consistent associations were observed for supraventricular tachycardia. Particulates were significantly associated with decreased ambulatory heart rate variability only in the 20 participants using ACE inhibitors.

Conclusions: Although these data support the hypothesis that particulate exposures may increase the risk of ventricular tachycardia for elderly people with coronary artery disease, heart rate variability was not associated with exposure in most of our participants. These results are

coherent with previous findings in this cohort for systemic inflammation, blood pressure, and ST

segment depression.

Introduction

Decreased heart rate variability (HRV) has been associated with cardiac morbidity and mortality and is often used as a marker of autonomic dysfunction and in the assessment of the impact of air pollution on cardiac autonomic control (Link and Dockery 2010). Associations also have been found between HRV and ischemia in coronary artery disease (CAD) patients monitored with ambulatory electrocardiograms (ECGs), including asymptomatic ST segment depression indicative of cardiac ischemia (Vardas et al. 1996). Given that many patients with CAD already have decreased HRV, pollutant exposures that lead to further HRV decreases might be expected to precipitate adverse clinical events such as ventricular tachycardia, and myocardial ischemia and infarction. Indeed, a number of recent air pollution studies have focused on CAD patients, though with mixed findings regarding associations between air pollutants and HRV (Barclay et al. 2009, Folino et al. 2009; Hampel et al. 2010; Schneider et al. 2010; Zanobetti et al. 2010). Nevertheless, a recent review of the literature on particulate air pollution and cardiovascular outcomes concluded that there was strong epidemiological evidence for an association between decreased HRV and short-term exposures to particulate matter (PM) air pollution in various populations, with the most consistent findings in older or clinically susceptible populations (Brook et al. 2010).

In contrast, the same literature review concluded that there was limited or weak epidemiological evidence for associations of cardiac arrhythmia with short-term exposures to PM (Brook et al. 2010). Another review suggested that there was evidence of an association of PM with cardiac arrhythmias, particularly ventricular arrhythmias, in patients with underlying cardiac disease (Link and Dockery 2010). Studies published since those reviews had mixed results: He et al. (2011) reported a significant association between personal $PM_{2.5}$ exposure and premature

5

ventricular contractions among 105 middle-aged participants using ambulatory ECGs, but only among participants without cardiovascular disease, and Mills et al. (2011) reported no "serious arrhythmias" or HRV effects in a randomized trial of dilute diesel exhaust exposure with 52 middle-aged participants. Little is known about possible mechanisms for PM effects on arrhythmia, though altered HRV, repolarization abnormalities, oxidative stress, and myocardial ischemia have been proposed as contributing factors (Link and Dockery 2010).

Between 2005 and 2007 we conducted a cohort panel study of acute cardiovascular outcomes with home-based ambient air pollution monitoring in the Los Angeles air basin, where ambient air pollution is dominated by mobile sources. Our focus was on traffic-related ultrafine particles, which are particularly high in redox-active chemical components (Ayres et al. 2008; Verma et al. 2009) that are hypothesized to induce arrhythmias via lipid peroxidation, endothelial dysfunction, and other mechanisms involving oxidative stress (Griendling and FitzGerald 2003). The present study used data from the same Los Angeles cohort to study the hypothesis that increased cardiac arrhythmia and decreased heart rate variability are associated with exposure to PM.

Methods

Study Population

We made repeated ambulatory ECG measurements among 55 elderly nonsmokers with CAD recruited from four retirement communities in the Los Angeles air basin. Eligibility criteria included age of at least 65 years, history of coronary artery disease, being a nonsmoker, and no exposure to environmental tobacco smoke. Coronary artery disease diagnoses were obtained by questionnaire or cardiologist interview, and confirmed with medical records review as described

previously (Delfino et al. 2008). Study cardiologists and nurses clinically evaluated 105 potentially eligible participants in our mobile medicine clinic. Twenty-one participants were not eligible to participate in the overall study, 18 dropped out of the ambulatory ECG monitoring portion of the study, and four had insufficient ambulatory ECG monitoring time ($\leq$ 3 days). Twelve participants with pacemakers also were excluded since pacemakers can render arrhythmia and HRV data invalid, leaving 50 participants and 8,952 hours of data. We confirmed the presence and absence of pacemakers using baseline ECG and ambulatory ECG data, and used digital and paper diaries to monitor daily medication use.

This study was approved by the institutional review board of the University of California, Irvine, in 2003. All participants gave informed consent.

Ambulatory ECG Monitoring and Outcomes

Each subject wore ambulatory ECG (Holter) monitors for two 5-day periods (Sunday through Friday) during their 12 weeks of follow-up, including one 5-day period between July and mid-October and one 5-day period between mid-October and February. We used the Burdick model 92513 Compact Digital Holter Recorder and Scanner/Software System (Burdick Inc., Deerfield, WI), which is a 7-lead 3-channel Holter ECG that has a data acquisition speed of 200 Hz. Each day, the subject removed leads and bathed before a trained research assistant arrived at the subject's home to download ECG data and setup the ECG for a new day. The Holter ECG signals (3 channels) were read and analyzed by Burdick Vision Premier Holter Analysis System, which includes algorithms for QRS labeling, arrhythmia detection, artifact identification and data correction. A Holter technician from the Noninvasive Laboratory of the University of California

Medical Center then screened the data for artifacts and outliers; indications of abnormalities, arrhythmias, ST segment changes and flagged ECG regions were reviewed by physicians.

Arrhythmia outcomes included supraventricular and ventricular arrhythmias in consecutive runs of ≥ 3 ectopic beats at a rate ≥ 120 beats per minute (Berger et al. 2006). The duration of arrhythmias and the number of foci in each hour were recorded. Numbers of arrhythmia events during 24-hour intervals corresponding to the gravimetric particle mass sampling times (afternoon to afternoon) also were recorded. The Holter output for each episode of supraventricular (atrial) tachycardia (SVT) and ventricular tachycardia (VT) was extracted. We defined SVT as paroxysmal supraventricular tachycardia (observed in N=460 subject-hours with one or more foci), and VT as single focus ventricular tachycardia (N=69 subject-hours) or multifocal ventricular tachycardia (N=232 subject-hours). Atrial fibrillation (N=2 subject-hours), atrial flutter (N=2 subject-hours), atrioventricular block (N=12 subject-hours), and accelerated idioventricular rhythm (N=50 subject-hours) were observed too infrequently analyze; we calculated subject-hours including SVT or VT without regard to these rare events.

We used Burdick Vision Series HRV software to analyze the QRS annotation file described above. All HRV measures were derived from 5-min epochs using acceptable normal-to-normal (NN) intervals (Task Force 1996). Only beats classified as normal and not preceded by ectopic beats or prolonged RR intervals were included in the NN interval estimation. An interpolation algorithm using cubic splines was used to replace missing beats, including the removed ectopic beats and artifacts, PVCs, and other non-normal R-R areas (Albrecht 1988). NN intervals <300 and or >3,000 ms or with NN ratios between < 0.8 or > 1.2 were rejected. Segments in which more than 20% of RR intervals required replacement were excluded from the analysis.

The HRV outcomes consisted of standard time domain variables (Task Force 1996) measured at the hourly level: standard deviation of normal R-R intervals (SDNN), root mean square of the successive differences between R-R intervals (r-MSSD), and logit percentage of adjacent normal R-R intervals that differed by >50 ms (logit pNN50). HRV outcomes were computed both for 1-hour intervals and for 24-hour intervals spanning the pollutant sampling periods (described below). However, day/night differences in NN intervals can contribute to a major fraction of the SDNN magnitude (Kleiger et al 2005). Therefore, for pollutants that were measured hourly, we also conducted analyses stratified according to daytime (06:00 to 19:00) and nighttime (19:00 to 06:00) periods.

The distributions of SDNN, r-MSSD, and pNN50 were moderately right skewed. WAfter removing some extreme outliers, we used three times the median of the absolute deviations of each SDNN or r-MSSD measurement from their median as a cutpoint for further removal of outliers (Zanobetti et al. 2010). This resulted in a loss of approximately 11% of hourly SDNN records and 13% of hourly r-MSSD records. The logit transformation was used for pNN50 with 2.27% of the hourly pNN50 records excluded due to pNN50 = 0.

Environmental Exposures

We monitored outdoor air pollutants using a specially equipped trailer parked at each retirement community. Hourly particle exposures for the analysis of both hourly and 24-hr HRV outcomes included total particle number concentrations (Condensation Particle Counter model 3785; TSI Inc, Shoreview, MN), $PM_{2.5}$ black carbon (BC, Aethalometer; Magee Scientific, Berkeley, CA), $PM_{2.5}$ organic and elemental carbon (OC-EC Analyzer model 3F; Sunset Laboratory Inc, Tigard, OR) (Arhami et al. 2006), and $PM_{2.5}$ mass using a Beta-Attenuation Mass (BAM) Monitor

(model 1020; Met One instruments Inc, Grants Pass, OR). The particle counter detects particle sizes ranging from 5 to over 3000 nm. We measured hourly pollutant gases including ozone (O_3), and markers of fossil fuel combustion, namely carbon monoxide (CO) and nitrogen oxides (NO_x), using federal reference methods (US Environmental Protection Agency, 2013). BC and EC are similar but not identical measurements of carbon linked to fossil fuel combustion.

We used the Sioutas™ Personal Cascade Impactor Sampler (SKC, Inc., Eighty Four, PA), to measure daily size-fractionated PM mass concentrations (Misra et al. 2002). The analysis included particles 0-0.25 μm in diameter ($PM_{0.25}$), accumulation mode particles 0.25-2.5 μm in diameter ($PM_{0.25-2.5}$), and coarse mode particles 2.5-10 μm in diameter ($PM_{2.5-10}$). $PM_{0.25}$ is considered "quasi-ultrafine" because the traditional cutpoint for the ultrafine mode is around 0.1 to 0.2 μm. Meteorological data were also collected in the air sampling trailer.

We estimated the mass of total organic carbon (OC) attributed to secondary OC (a surrogate of photochemically-derived OC) and the mass of OC attributed to primary OC (attributable to primary combustion sources, mostly traffic in the study regions). These estimates were based on the EC tracer method and are described elsewhere (Polidori et al. 2007).

Personal Accelerometer Data

Given the inverse relationship between physical activity and vagal influences on the heart during high levels of activity (Grossman 2004, 2007), it is possible that associations between air pollution and ambulatory HRV could be confounded or modified by different activity levels, especially respiratory sinus arrhythmia as reflected by r-MSSD or pNN50. As such, we electronically monitored physical activity continuously for each 24-hr period with a personal motion logger (Mini-motionlogger, Ambulatory Monitoring, Inc., Ardsley, NY), a piezoelectric

accelerometer. The accelerometer recorded objective measurements of movement intensity using the unit's high sensitivity proportional integrating measure mode. We discarded accelerometer data at the beginning and end of each daily sampling period to avoid movement artifacts from equipment removal and setup. Valid accelerometer data were available for 92.8% of all hourly ECG records. We normalized 1-minute data by subject-specific Z-scores, and then determined average movement intensity for hourly periods corresponding to hourly periods for the HRV and arrhythmia data.

Statistical Analysis

Statistical analyses were conducted using SAS software. Regression models were used to estimate associations between HRV and arrhythmia outcomes with interquartile range (IQR) increases in individual pollutants adjusted for potential confounding variables. Generalized estimating equations (implemented in PROC GENMOD) were used to account for within-subject correlations induced by the repeated measures design. A Gaussian variance structure was assumed for continuous HRV outcomes (SDNN, rMSSD, and logit pNN50). For arrhythmia outcomes (VT and SVT), quasi-Poisson variance was assumed for daily counts, and quasi-binomial variance was assumed for the absence/presence of VT or SVT events during hourly intervals. Auto-regressive correlation was assumed for residual errors from the same individual. For analyses of daily VT counts, we excluded data from one participant with >19 VT events per day during the warm season phase because they were highly influential (Cook's D > 0.3). In addition we excluded VT data from 8 other participants with values > 3 SD above the mean.

We estimated odds ratios for the occurrence of one or more arrhythmia events during hourly intervals in association with pollutant concentrations during the hour before the outcome

measurement, and with average pollutant concentrations during the 4 hours, 8 hours, 24 hours, 3 days, and 5 days before the outcome. We estimated daily rate ratios associated with size-fractionated PM exposures ($PM_{0.25}$, $PM_{0.25-2.5}$, and $PM_{2.5-10}$) averaged during the current 24-hr interval (lag 0) and the previous 24-hr interval (lag 1, 25-48-hour average), and averaged over 2-days (during the current and previous 24-hrs). Longer average exposures or lags greater than one day could not be assessed for PM fractions because PM filters were collected during the 5 days of Holter monitoring only. Both the risk of VT (e.g., Lampert et al. 1994) and air pollutant exposures (Polidori et al. 2007) are well known to differ between daytime and nighttime hours, leading us to investigate modification of pollutant associations with VT by daytime/nighttime hours as an *a priori* hypothesis. Thus we fit additional models stratified by this variable and conducted formal hypothesis tests using Cochran's Q statistic (Cochran, 1954) to assess the significance of differences in daytime vs. nighttime associations.

In secondary analyses, we used interaction terms to test for effect modification by sex, medication use, and self-reported co-morbidities. For VT we also repeated the analyses excluding daytime hours in which participants reported they were away from home.

All effect estimates were adjusted for hourly or daily average actigraph-derived physical activity and heart rate, temperature averaged over the exposure time period, day of week, 5-day study period (July to mid-October or mid-October through February), and retirement community. Exposures were decomposed using the Sheppard et al. (2005) mean-centering approach to implicitly adjust for potential confounding and mismeasurement of exposure by study phase and retirement community (see Supplemental Material). Hour of day also was investigated as a possible confounder, but omitted from final models due to lack of evidence of any confounding (i.e., little change in model coefficients). Statistical significance was assessed using a 5% type I

error rate per test, and 95% confidence intervals are reported for point estimates. Due to the relatively large number of tests conducted (multiple pollutants, multiple outcomes, and multiple lag times), the percentage of tests yielding significant associations is reported for major categories of comparisons.

Results

Nearly half of the study participants had a previous myocardial infarction; the remainder qualified for enrollment based on coronary artery bypass graft or angioplasty, a positive angiogram or stress test, or clinical diagnosis of CAD (Table 1). In addition, most (68%) had hypertension and nearly all (76%) had hypercholesterolemia. 62% were male and most participants were overweight (the mean body mass index was 27, and 20% were obese). Cardiac medications were common, the majority taking β-adrenergic blocking agents or hypocholesterolemic agents such as statins. Although the four retirement communities were non-smoking facilities and none of the participants were current or recent smokers (within 12 months), 44% were former smokers.

Summary statistics for the outcome variables are shown in Table 2. pNN50 was similar during day and night, but SDNN and rMSSD were higher during daytime hours than at night.

Pollutant measurements are described in Table 3. Because 2-3 participants in the same retirement community were simultaneously monitored on each day, the number of 24-hour pollutant measurements (n=235) is less than the 500 measurements that would have resulted from measuring each participant's personal exposure. Regression effect estimates were standardized to the IQR of each pollutant. The traffic-related air pollutants (primary OC, NO_x,

CO) were highly positively correlated with each other, with pairwise Spearman correlations ≥ 0.75, whereas O_3 was negatively correlated and secondary OC was not correlated with these primary combustion-related pollutants (Supplemental Material, Table S1). Given the strong correlation among primary pollutants, our regression models test one pollutant at a time.

Associations between daily count of VT events and outdoor air pollutants, adjusting for confounding variables, are shown in Table 4. An IQR increase in 24-hr average $PM_{2.5}$ was associated with a 50% increase in the daily rate of VT events (95% CI: 2% to 120%). The estimated effect of 3-day average $PM_{2.5}$ on daily VT was nearly identical, though not statistically significant. Analysis of $PM_{2.5}$ constituents indicated statistically significant associations between daily VT and average exposures during the previous 24-hours for BC, EC, total OC, and primary OC. Average total OC during the previous 24-h was strongly associated with daily VT (RR = 3.06; 95% CI: 1.82, 5.17 per IQR increase), with the strongest constituent-specific association being with primary OC and a relatively weak association with secondary OC. Ozone also was strongly associated with daily VT, particularly the 3-day average (RR = 2.95; 95% CI: 1.29, 6.74). Associations between size fractionated PM and daily VT varied by averaging time, ranging from a 0% to 31% increase for $PM_{0.25}$ and $PM_{0.25-2.5}$, and from a 13% decrease to 20% increase for $PM_{2.5-10}$. When the outlying subject with >19 events per day was included RRs for VT events were mostly larger than reported here, often exceeding 5 with wide confidence intervals (data not shown).

Table 4 also shows odds ratios for hourly daytime and nighttime models using occurrence of one or more VT events per hour as the outcome variable. In these models daytime VT risk was positively associated with IQR increases in $PM_{2.5}$ concentrations for all averaging times, but none of the associations were statistically significant. Nighttime VT risk actually decreased with

14 -

IQR increases in $PM_{2.5}$ concentrations at averaging times shorter than 3 days, but again these associations were not statistically significant. Among PM constituents, BC and OC had the strongest associations with VT during the daytime and were significantly elevated across a variety of averaging times. NO_x, a marker of primary combustion products, was positively associated with daytime VT for averaging times greater than 4 hours, but only the 5-day averaging time was statistically significant. In contrast, hourly nighttime VT was often negatively associated with PM constituents, to the extent that several formal tests of daytime-nighttime heterogeneity were statistically significant for 8- and 24-hr average exposures.

A mixture of daytime and nighttime positive associations were found for VT and O_3. Daytime associations were positive at 1-hr, 4-hr, and 8-hr but negative 24-hr, 3-day, and 5-day. In contrast, nighttime associations were nearly null at 1-hr and 4-hr and positive at 8-hr, 3-day, and 5-day. The inverse associations for 24-hr, 3-day, and 5-day O_3 in daytime were unexpected..

In secondary analyses we tested other potential subject-specific effect measure modifiers but found no consistent differences in associations of VT with air pollutants according to sex, diabetes, obesity (body mass index $\geq$ 30), and medication classes added to the model individually (anti-arrhythmic medications, beta-blockers, digitalis and other inotropic agents, statins, and ACE inhibitors) (data not shown). Although our panel study design was well powered to investigate associations with pollutants and interaction effects with stress and other time-varying characteristics, with only 50 participants it had little power to detect effect modification by sex, co-morbidities, medications, and other time-invariant characteristics. We also repeated the VT analyses excluding daytime hours during which the participants reported being away from home (9% of daytime hours); results were very similar to those in Table 4 (data not shown).

15

Few significant associations were found between SVT and PM variables in either the daily or hourly models: none of 72 tests were significant at the 1% level, and only 2 tests (2.8%) were significant at the 5% level (Supplemental Material, Table S2). Notably, these 2 "significant" associations occurred at a rate near the expected 5% false positive rate for these tests under a null hypothesis of no associations. Among 27 tests for gaseous pollutants, there were four statistically significant decreases in SVT (for 3-day O_3, 4-hr NO_x, 1-hr CO, and 4-hr CO) and the only statistically significant increases in SVT were for IQR increases in 4-hr (RR = 1.19; 95% CI: 1.02, 1.39) and 8-hr ozone (RR = 1.25; 95% CI: 1.00, 1.56).

Few significant associations were estimated for PM variables and the three hourly HRV outcomes (SDNN, rMSSD, and logit pNN50): none of 126 tests were significant at the 1% level, and only 6 tests (4.8%) were significant at the 5% level (Supplemental Material, Table S3). In contrast, the 54 tests for outdoor gaseous pollutants (O_3, NO_x, and CO) with hourly HRV yielded 3 significant associations (5.6%) at the 1% level, and 9 significant associations (16.7%) at the 5% level, primarily showing unexpected increases in HRV associated with IQR increases in NO_x and CO exposure at 4- to 8-hr lags. Similarly, daily lag 0, 1 and 2-day average size-fractionated PM mass concentrations also were not significantly associated with 24-hour SDNN (data not shown).

We tested potential effect measure modification of air pollutant effects on 4-hr, 8-hr, and 1-day SDNN by medication use and found no significant differences except for ACE inhibitors. 8-hr $PM_{2.5}$, 8-hr BC, 4-hr secondary OC, and 4-hr and 8-hr ozone were significantly and inversely associated with hourly SDNN only among the 20 participants taking ACE inhibitors (Figure 1). In contrast, 4-hr and 8-hr EC, 8-hr BC, and 8-hr OC were significantly and positively associated with hourly SDNN among the participants not taking ACE inhibitors.

Discussion

Prior to 2005 few studies of HRV and air pollution monitored participants using ambulatory ECG. Instead, most studies recorded short ECG strips at rest during in-clinic visits to control for effects of physical activity on respiratory sinus arrhythmia (Delfino et al. 2005). The present study opted for activity-adjusted ambulatory ECG collected during two 5-day intervals for each participant along with detailed home air pollutant monitoring, which allowed estimation of PM and PM constituent effects on both HRV and cardiac arrhythmias.

Apart from participants taking ACE inhibitors, these data do not show convincing associations between outdoor pollutants and HRV or SVT after adjusting for likely confounding variables. We believe that our community-based exposure measurements are more accurate and our confounding controls are as good or better than those used in previous investigations, which often relied on ambient pollutant monitoring at central sites and lacked actigraph physical activity data. We recognize, however, that outdoor air pollutant concentrations measured at home are only a surrogate for personal exposure since they do not capture air pollutant exposures during time spent away from the home or indoor pollutant sources. VT associations with pollutants were similar when diary-reported hours away from home were excluded, suggesting that time spent away from home is not a confounder in this setting.

Barclay et al. (2009) suggested that the use of beta-blockers and other cardiac medications, like digitalis, which is vagotonic, may mitigate adverse effects of PM on HRV. Consistent with this possibility, de Hartog et al. (2009) observed associations between PM and reduced SDNN only in CAD patients not taking beta-blockers. However, we did not find any evidence that beta-

blockers or other cardiac medications modified associations between air pollutants and HRV, with the exception of ACE inhibitors.

We observed evidence of negative associations between air pollutants and SDNN among participants using ACE inhibitors, in contrast with null or positive associations with the same pollutants among non-users. A similar finding was reported in a recent ambulatory ECG study of 1607 participants age 50-72, in which 10-year average PM_{10} was associated with decreased HRV only among 97 participants taking ACE inhibitors (Adam et al. 2012). These findings may be related to the well-known side effect of ACE inhibitor-induced cough. Several mechanisms for this side effect have been proposed, including the accumulation in the airways of protussive mediators bradykinin and substance P that are degraded by ACE, and/or activation of bradykinin receptors on pulmonary rapidly adapting vagal afferents by ACE inhibitors (Dicpinigaitis et al. 2006; Hargreaves et al. 1992). Thus the apparent reduction in SDNN in response to air pollutant exposures among participants using ACE inhibitors might be explained by the stimulation of pulmonary vagal afferents by bradykinin, resulting in increased parasympathetic tone and decreased HRV.

We estimated strong associations between PM and VT in our participants. One study of patients with implantable cardiac defibrillators (ICDs) reported no association of VT with ambient air pollution (Metzger et al. 2007) whereas two others did (Dockery et al. 2005; Ljungman et al. 2008). Our participants (mean age: 83 years) were older than those in previous studies, and only one had an ICD (this subject had no VT events). Similarly, Folino et al. (2009) reported strong associations between PM and VT, but not HRV, in CAD patients in their Holter study. Another Holter study of CAD patients reported associations between PM exposures and VT, but did not report any findings on HRV (Berger et al. 2006). We previously reported that other clinically

important outcomes were associated with PM in our study participants, including blood pressure, ischemic ST segment depression, and markers of systemic inflammation and platelet activation that might contribute to PM-related cardiac electrical effects (Delfino et al. 2009, 2010a, 2010b, 2011).

Evidence of day/night effect modification of associations between VT and many pollutants might result from differences in indoor infiltration conditions and air pollutant composition between daytime and nighttime. For example, personal exposure to O_3 might differ substantially between the day and night due to use of air conditioning and reduced time outdoors during hotter daytime hours and greater exposure to outdoor air during cooler nighttime hours. This might explain the unexpected inverse association between VT and outdoor O_3 during the daytime. It might also reflect differences in cardiac response to air pollutants between waking and sleeping hours, though we do not know of any specific mechanism to explain this.

In conclusion, the present study supports the hypothesis that particulate air pollutant exposure increases the risk of ventricular tachycardia (consecutive runs of ≥ 3 ectopic beats at a rate ≥ 120 beats per minute) in a population of elderly people with coronary artery disease. An increased rate of arrhythmia at higher PM concentrations has direct medical relevance and strong support in the present study. However, decreased heart rate variability was not associated with air pollutants except in the subset of participants taking ACE inhibitors (n=20). Future panel studies on cardiac effects of PM exposure might benefit from assessment of other mechanisms in addition to HRV.

19

References

Adam M, Felber Dietrich D, Schaffner E, Carballo D, Barthélémy JC, Gaspoz JM, et al. 2012. Long-term exposure to traffic-related PM(10) and decreased heart rate variability: is the association restricted to subjects taking ACE inhibitors? Environ Int 48:9-16.

Albrecht P, Cohen RJ. 1988. Estimation of heart rate power spectrum bands from real-world data: Dealing with ectopic beats and noisy data. Comput Cardiol 15:311-314.

Arhami M, Kuhn T, Fine PM, Delfino RJ, Sioutas C. 2006. Effects of sampling artifacts and operating parameters on the performance of a semi-continuous particulate EC/OC monitor. Environ Sci Technol 40:945-953.

Ayres JG, Borm P, Cassee FR, Castranova V, Donaldson K, Ghio A, et al. 2008. Evaluating the toxicity of airborne particulate matter and nanoparticles by measuring oxidative stress potential--a workshop report and consensus statement. Inhal Toxicol 20:75-99.

Barclay JL, Miller BG, Dick S, Dennekamp M, Ford I, Hillis GS, et al. 2009. A panel study of air pollution in subjects with heart failure: negative results in treated patients. Occup Environ Med 66:325–334.

Berger A, Zareba W, Schneider A, Rückerl R, Ibald-Mulli A, Cyrys J, et al. 2006. Runs of ventricular and supraventricular tachycardia triggered by air pollution in patients with coronary heart disease. J Occup Environ Med 48:1149-1158.

Brook RD, Rajagopalan S, Pope CA 3rd, Brook JR, Bhatnagar A, Diez-Roux AV, et al. 2010. Particulate matter air pollution and cardiovascular disease: An update to the scientific statement from the American Heart Association. Circulation 121:2331-2378.

Cochran WG. 1954. The Combination of Estimates from Different Experiments. Biometrics 10:101-129.

de Hartog JJ, Lanki T, Timonen KL, Hoek G, Janssen NA, Ibald-Mulli A, et al. 2009. Associations between PM2.5 and heart rate variability are modified by particle composition and beta-blocker use in patients with coronary heart disease. Environ Health Perspect 117:105-111.

Delfino RJ, Sioutas C, Malik S. 2005. Potential Role of Ultrafine Particles in Associations between Airborne Particle Mass and Cardiovascular Health. Environ Health Perspect 113: 934–946.

Delfino RJ, Staimer N, Tjoa T, Polidori A, Arhami M, Gillen DL, et al. 2008. Circulating biomarkers of inflammation, antioxidant activity, and platelet activation are associated with primary combustion aerosols in subjects with coronary artery disease. Environ Health Perspect 116:898-906.

Delfino RJ, Staimer N, Tjoa T, Gillen D, Polidori A, Arhami M, et al. 2009. Air pollution exposures and circulating biomarkers of effect in a susceptible population: clues to potential causal component mixtures and mechanisms. Environ Health Perspect 117:1232–1238.

Delfino RJ, Staimer N, Tjoa T, Arhami M, Polidori A, George SC, et al. 2010a. Associations of primary and secondary organic aerosols with airway and systemic inflammation in an elderly panel cohort. Epidemiology 21:892-902.

Delfino RJ, Tjoa T, Gillen D, Staimer N, Polidori A, Arhami M, et al. 2010b. Traffic-related air pollution and blood pressure in elderly subjects with coronary artery disease. Epidemiology 21:396-404.

Delfino RJ, Gillen DL, Tjoa T, Staimer N, Polidori A, Arhami M, et al. 2011. Electrocardiographic ST-Segment Depression and Exposure to Traffic-Related Aerosols in Elderly Subjects with Coronary Artery Disease. Environ Health Perspect 119:196-202.

Dicpinigaitis PV. 2006. Potential future therapies for the management of cough: ACCP evidence-based clinical practice guidelines. Chest 129(1 Suppl):284S-286S.

Dockery DW, Luttmann-Gibson H, Rich DQ, Link MS, Mittleman MA, Gold DR, et al. 2005. Association of air pollution with increased incidence of ventricular tachyarrhythmias recorded by implanted cardioverter defibrillators. Environ Health Perspect 113:670-674.

Folino AF, Scapellato ML, Canova C, Maestrelli P, Bertorelli G, Simonato L, et al. 2009. Individual exposure to particulate matter and the short-term arrhythmic and autonomic profiles in patients with myocardial infarction. Eur Heart J 30: 1614-1620.

Griendling KK, FitzGerald GA. 2003. Oxidative Stress and Cardiovascular Injury Part II: Animal and Human Studies. Circulation 108: 2034-2040.

Grossman P, Taylor EW. 2007. Toward understanding respiratory sinus arrhythmia: relations to cardiac vagal tone, evolution and biobehavioral functions. Biol Psychol 74:263-285.

Grossman P, Wilhelm FH, Spoerle M. 2004. Respiratory sinus arrhythmia, cardiac vagal control, and daily activity. Am J Physiol Heart Circ Physiol 287:H728-734.

Hampel R, Schneider A, Bruske I, Zareba W, Cyrys J, Rückerl R, et al. 2010. Altered Cardiac Repolarization in Association with Air Pollution and Air Temperature among Myocardial Infarction Survivors. Environ Health Perspect 118:1755–1761.

Hargreaves M, Ravi K, Senaratne MP, Kappagoda CT. 1992. Responses of airway rapidly adapting receptors to bradykinin before and after administration of enalapril in rabbits. Clin Sci (Lond) 83:399-407.

He F, Shaffer ML, Rodriguez-Colon S, Yanosky JD, Bixler E, Cascio WE, et al. 2011. Acute Effects of Fine Particulate Air Pollution on Cardiac Arrhythmia: The APACR Study. Environ Health Perspect 119:927–932.

Kleiger RE, Stein PK, Bigger JT Jr. 2005. Heart rate variability: measurement and clinical utility. Ann Noninvasive Electrocardiol 10:88-101.

Lampert R, Rosenfeld L, Batsford W, Lee F, McPherson C. 1994. Circadian variation of sustained ventricular tachycardia in patients with coronary artery disease and implantable cardioverter-defibrillators. Circulation 90:241-247.

Link MS, Dockery DW. 2010. Air pollution and the triggering of cardiac arrhythmias. Curr Opin Cardiol 25:16–22.

Ljungman PLS, Berglind N, Holmgren C, Gadler F, Edvardsson N, Pershagen G, et al. 2008. Rapid effects of air pollution on ventricular arrhythmias. Eur Heart J 29: 2894–2901.

Metzger KB, Klein M, Flanders WD, Peel JL, Mulholland JA, Langberg JJ, et al. 2007. Ambient Air Pollution and Cardiac Arrhythmias in Patients With Implantable Defibrillators. Epidemiology 18: 585-592.

Mills NL, Finlayson AE, Gonzalez MC, Törnqvist H, Barath S, Vink E, et al. 2011. Diesel exhaust inhalation does not affect heart rhythm or heart rate variability. Heart 97: 544-550.

Misra C, Singh M, Hall P, Sioutas C. 2002. Development and evaluation of a personal cascade impactor sampler (PCIS). J Aerosol Science 33:1027-1047.

Polidori A, Arhami M, Delfino RJ, Allen R, Sioutas C. 2007. Indoor-outdoor relationships, trends and carbonaceous content of fine particulate matter in retirement communities of the Los Angeles basin. J Air Waste Manage Assoc 57:366-379.

Schneider A, Hampel R, Ibald-Mulli A, Zareba W, Schmidt G, Schneider R, et al. 2010. Changes in deceleration capacity of heart rate and heart rate variability induced by ambient air pollution in individuals with coronary artery disease. Particle and Fibre Toxicology 7:29.

Sheppard L, Slaughter JC, Schildcrout J, Liub LJS, Lumley T. 2005. Exposure and measurement contributions to estimates of acute air pollution effects. J Expos Anal Environ Epidemiol 15: 366-376.

Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. 1996. Heart rate variability: Standards of measurement, physiological interpretation, and clinical use. Circulation 93:1043-1065.

US Environmental Protection Agency. 2013. List of Designated Reference and Equivalent Methods. Available: http://www.epa.gov/ttnamti1/files/ambient/criteria/reference-equivalent-methods-list.pdf [accessed 30 June 2013].

Vardas, PE, Kochiadakis GE, Manios EG, Kanoupakis EM, Zouridakis EG, Chlouverakis GI. 1996. Spectral analysis of heart rate variability before and during episodes of nocturnal ischaemia in patients with extensive coronary artery disease. Eur Heart J 17:388-393.

Verma V, Polidori A, Schauer JJ, Shafer MM, Cassee FR, Sioutas C. 2009. Redox activity of urban quasi-ultrafine particles from primary and secondary sources. Atmos Environ 43:6360-6368.

Zanobetti A, Gold DR, Stone PH, Suh HH, Schwartz J, Coull BA, et al. 2010. Reduction in Heart Rate Variability with Traffic and Air Pollution in Patients with Coronary Artery Disease. Environ Health Perspect 118:324–330.

Table 1. Characteristics of participants (N=50) -

Characteristic		Mean ±SD or N (%)
Age (years)		83.3 ± 5.95
BMI (kg/m^2)		27.0 ± 3.63
Obese (BMI >30)		(10) 20%
Sex	Male	31 (62%)
	Female	19 (38%)
Cardiovascular History	Confirmation of CAD:[a]	
	Myocardial infarction	23 (46%)
	Coronary artery bypass graft or angioplasty	16 (32%)
	Positive angiogram or stress test	8 (16%)
	Clinical diagnosis[b]	3 (6%)
	Current angina pectoris	14 (28%)
	Cardiac arrhythmia	10 (20%)
	Congestive heart failure	10 (20%)
	Hypertension	34 (68%)
	Hypercholesterolemia	38 (76%)
Other Medical History:	Type II diabetes	7 (14%)
	COPD or asthma	5 (10%)
	Stroke or transient ischemic attack	8 (16%)
Medications:	β-adrenergic blocking agents	30 (60%)
	Anti-arrhythmic drugs	4 (8%)
	Digoxin	3 (6%)
	ACE inhibitors	20 (40%)
	HMG-CoA reductase inhibitors (statins)	27 (54%)
	Platelet aggregation inhibitors or Coumadin	17 (34%)
	Calcium channel blockers	17 (34%)
	At least one of the following medications: a beta-blocker, a calcium channel blocker, or an anti-arrhythmic drug having beta-blocker and/or calcium channel antagonistic effects	37 (74%)
Smoking history:	Never smoker	28 (56%)
	Ex-smoker (no smoking within 12 months)	22 (44%)

[a] Each category is hierarchical - excludes being in above diagnostic category

[b] Coronary microvascular disease

ACE: angiotensin I-converting enzyme

HMG-CoA: 3-Hydroxy-3-methylglutaryl coenzyme A

Table 2. Distribution of outcome variables -

Outcome	Mean ± SD	Median	Min	Max
VT (ventricular tachycardia) [a]				
24-hr Count	1.73 ± 11.14	0	0	158
SVT (supraventricular tachycardia) [b]				
24-hr Count	1.32 ± 3.46	0	0	36
SDNN (hourly standard deviation of normal R-R intervals in ms)				
Day & Night [c]	72.91 ± 34.98	66	3	159
Daytime	74.26 ± 34.19	68	6	159
Nighttime	69.92 ± 36.50	62	3	159
rMSSD (hourly root mean square of successive differences in ms)				
Day & Night [c]	49.25 ± 45.67	29	0.06	183
Daytime	50.32 ± 46.71	29	0.06	183
Nighttime	46.88 ± 43.18	29	0.11	183
pNN50 (hourly percent of normal R-R interval differences > 50 msec)				
Day & Night [c]	22.4 ± 28.7	5.76	0	97.3
Daytime	22.5 ± 28.4	5.85	0	91.5
Nighttime	22.4 ± 28.9	5.65	0	97.3

[a] We observed VT events in 301 hourly periods among 18 participants -

[b] We observed SVT events in 460 hourly periods among 39 participants. 13 of those participants also - experienced VT events. -

[c] Daytime is 06:00 to 19:00, and nighttime is 19:00 to 06:00. -

Table 3. Distribution of outdoor air pollution variables -

Exposure (24-hr averages)[a]	N	N missing [a]	Mean ± SD	IQR	Min	Max
Continuously-measured PM:						
$PM_{2.5}$ (μg/m³)[b]	235	0	21.1 ± 11.4	16.1	2.3	77.4
Particle number (no./cm³)	184	51	12,818 ± 5,889	6,351	2,019	30,180
Black carbon (μg/m³)	235	0	1.7 ± 0.8	1.0	0.3	4.5
Elemental carbon (μg/m³)	198	37	1.52 ± 0.6	0.9	0.3	3.3
Organic carbon (OC) (μg/m³)	188	47	7.8 ± 3.7	5.2	2.5	18.7
Primary OC (μg/m³)	157	78	5.3 ± 2.9	4.4	41.4	12.6
Secondary OC (μg/m³)	157	78	2.9 ± 1.5	2.1	0.3	7.7
Size-fractionated PM[b]:						
$PM_{0.25}$ (μg/m³)	217	18	9.8 ± 4.1	7.0	2.5	30.1
$PM_{0.25-2.5}$ (μg/m³)	226	9	11.4 ± 9.4	10.6	1.0	66.8
$PM_{2.5-10}$ (μg/m³)	217	18	9.4 ± 5.0	5.5	0.3	24.6
Criteria pollutant gases:						
NO_x (ppb)	235	0	46.6 ± 31.4	42.3	3.2	183.7
CO (ppm)	224	11	0.53 ± 0.30	0.42	0.01	1.68
O_3 (ppb)	232	3	27.1 ± 11.5	17.4	3.8	60.7

[a]The continuously-measured PM variables were averaged hourly and we present 24-hour averages here. There were fewer missing observations for black carbon, $PM_{2.5}$ and the gases because two samplers were operated in parallel at all times. There was more missing primary and secondary OC than total OC because of missing predictor data used to estimate these two OC fractions, including elemental carbon.
[b]We measured $PM_{2.5}$ mass was hourly with a pair of Beta-Attenuation Mass Monitors whereas we measured the size-fractionated PM mass daily with a Personal Cascade Impactor Sampler, which had more missing data.

Table 4. Associations[a] of ventricular tachycardia with outdoor air pollutants, per IQR

Exposure and averaging time	Daily RR (95% CI)	Hourly daytime[c] OR (95% CI)	Hourly nighttime[b] OR (95% CI)	P-value for OR heterogeneity[c]
$PM_{2.5}$				
1-hr	--	1.06 (0.83, 1.35)	0.94 (0.60, 1.47)	0.645
4-hr	--	1.21 (0.95, 1.54)	0.94 (0.56, 1.58)	0.391
8-hr	--	1.17 (0.95, 1.44)	0.86 (0.51, 1.45)	0.284
24-hr	1.50 (1.02, 2.20)**	1.23 (0.99, 1.52)*	0.85 (0.64, 1.12)	0.039**
3-day	1.51 (0.85, 2.70)	1.26 (0.99, 1.61)*	1.19 (0.84, 1.67)	0.778
5-day	1.16 (0.59, 2.29)	1.30 (0.78, 2.17)	2.15 (0.90, 5.11)*	0.328
Particle number				
1-hr	--	1.06 (0.86, 1.30)	0.77 (0.59, 1.01)*	0.071*
4-hr	--	1.05 (0.84, 1.31)	0.90 (0.62, 1.30)	0.491
8-hr	--	0.90 (0.64, 1.26)	1.09 (0.70, 1.70)	0.506
24-hr	0.70 (0.41, 1.20)	0.90 (0.55, 1.46)	0.64 (0.31, 1.31)	0.442
3-day	0.42 (0.09, 1.94)	1.16 (0.41, 3.26)	0.70 (0.26, 1.92)	0.497
5-day	0.20 (0.02, 1.67)	2.43 (0.55, 10.7)	0.88 (0.10, 7.89)	0.453
Black carbon				
1-hr	--	1.07 (0.94, 1.22)	0.84 (0.53, 1.34)	0.327
4-hr	--	1.07 (0.91, 1.25)	0.75 (0.44, 1.29)	0.215
8-hr	--	1.23 (1.06, 1.44)#	0.69 (0.46, 1.03)*	0.008#
24-hr	1.40 (1.06, 1.84)**	1.30 (0.98, 1.72)*	0.74 (0.54, 1.00)*	0.008#
3-day	1.59 (0.77, 3.30)	1.88 (1.30, 2.73)#	1.38 (0.78, 2.42)	0.365
5-day	1.36 (0.64, 2.91)	2.68 (1.32, 5.42)#	2.63 (0.87, 8.00)*	0.978
Elemental carbon				
1-hr	--	1.01 (0.92, 1.11)	0.79 (0.56, 1.11)	0.181
4-hr	--	0.96 (0.85, 1.08)	0.80 (0.47, 1.35)	0.507
8-hr	--	1.09 (0.92, 1.30)	0.63 (0.38, 1.06)*	0.049**
24-hr	1.55 (1.09, 2.21)**	1.24 (0.95, 1.60)	0.69 (0.50, 0.96)**	0.006#
3-day	1.46 (0.65, 3.30)	2.10 (1.08, 4.09)**	1.09 (0.54, 2.22)	0.187
5-day	1.90 (0.82, 4.37)	3.07 (0.90, 10.5)*	1.57 (0.69, 3.58)	0.375
Organic Carbon (OC)				
1-hr	--	1.24 (0.78, 1.97)	0.91 (0.49, 1.68)	0.431
4-hr	--	2.13 (1.31, 3.49)#	0.84 (0.38, 1.86)	0.051*
8-hr	--	2.58 (1.47, 4.52)#	0.65 (0.23, 1.81)	0.021**
24-hr	3.06 (1.82, 5.17)#	1.81 (1.08, 3.06)**	0.57 (0.19, 1.69)	0.060*
3-day	2.13 (0.60, 7.51)	2.76 (0.40, 19.02)	1.73 (0.65, 4.65)	0.673
5-day	5.95 (0.79, 44.8)*	4.22 (0.25, 71.7)	3.13 (0.25, 38.6)	0.877
Primary OC				
1-hr	--	0.85 (0.65, 1.13)	0.89 (0.54, 1.46)	0.888
4-hr	--	0.93 (0.62, 1.39)	0.91 (0.44, 1.88)	0.966
8-hr	--	1.07 (0.54, 2.09)	0.64 (0.30, 1.37)	0.326
24-hr	2.64 (1.13, 6.21)**	1.90 (0.64, 5.61)	0.99 (0.34, 2.86)	0.400
3-day	2.16 (0.69, 6.77)	2.07 (0.57, 7.55)	0.78 (0.31, 1.98)	0.231
5-day	3.15 (0.30, 33.3)	11.2 (0.49, 258)	0.62 (0.07, 5.51)	0.137
Secondary OC				
1-hr	--	1.18 (0.90, 1.54)	1.12 (0.76, 1.66)	0.833
4-hr	--	1.68 (1.21, 2.33)#	1.24 (0.76, 2.02)	0.307
8-hr	--	1.86 (1.06, 3.26)**	1.31 (0.90, 1.90)	0.301
24-hr	1.43 (0.93, 2.18)*	1.18 (0.69, 2.02)	1.45 (0.70, 3.00)	0.653

Exposure and averaging time	Daily RR (95% CI)	Hourly daytime[c] OR (95% CI)	Hourly nighttime[b] OR (95% CI)	P-value for OR heterogeneity[c]
3-day	1.28 (0.47, 3.47)	0.68 (0.20, 2.30)	2.30 (0.41, 13.0)	0.261
5-day	2.27 (0.79, 6.58)	0.97 (0.22, 4.15)	1.68 (0.54, 5.23)	0.558
$PM_{0.25}$				
Lag 0 (24-hr)	1.04 (0.67, 1.60)	--	--	
Lag 1 (25-48 hr)	1.20 (0.97, 1.47)*	--	--	
2-day	1.29 (0.73, 2.29)	--	--	
$PM_{0.25-2.5}$				
Lag 0 (24-hr)	1.31 (1.05, 1.64)**	--	--	
Lag 1 (25-48 hr)	1.00 (0.78, 1.28)	--	--	
2-day	1.30 (0.96, 1.77)*	--	--	
$PM_{2.5-10}$				
Lag 0 (24-hr)	1.20 (0.90, 1.59)	--	--	
Lag 1 (25-48 hr)	0.87 (0.71, 1.06)	--	--	
2-day	0.97 (0.66, 1.44)	--	--	
O_3				
1-hr	--	1.33 (1.09, 1.62)#	0.98 (0.66, 1.47)	0.184
4-hr	--	1.37 (1.06, 1.77)**	0.99 (0.64, 1.53)	0.213
8-hr	--	1.37 (0.98, 1.91)*	1.13 (0.74, 1.70)	0.472
24-hr	1.60 (1.12, 2.30)**	0.66 (0.35, 1.25)	2.68 (1.32, 5.46)#	0.004#
3-day	2.95 (1.29, 6.74)**	0.30 (0.08, 1.14)*	1.43 (0.45, 4.57)	0.082*
5-day	0.93 (0.10, 8.16)	0.05 (0.01, 0.53)**	2.05 (0.42, 9.86)	0.010**
NO_x				
1-hr	--	0.98 (0.75, 1.29)	1.13 (0.72, 1.78)	0.585
4-hr	--	0.99 (0.77, 1.27)	0.92 (0.55, 1.54)	0.800
8-hr	--	1.15 (0.90, 1.47)	0.67 (0.35, 1.27)	0.120
24-hr	1.37 (0.99, 1.88)*	1.49 (0.85, 2.62)	0.54 (0.28, 1.03)*	0.021**
3-day	1.80 (0.45, 7.12)	2.90 (0.87, 9.68)*	1.00 (0.30, 3.30)	0.219
5-day	1.70 (0.54, 5.40)	7.98 (1.48, 43.0)**	1.34 (0.14, 13.1)	0.217
CO				
1-hr	--	1.03 (0.82, 1.30)	0.96 (0.66, 1.40)	0.730
4-hr	--	1.06 (0.84, 1.34)	0.79 (0.55, 1.15)	0.192
8-hr	--	1.11 (0.88, 1.39)	0.68 (0.47, 0.98)**	0.025**
24-hr	1.18 (0.84, 1.65)	0.84 (0.45, 1.56)	0.53 (0.32, 0.89)**	0.276
3-day	2.20 (0.82, 5.94)	1.03 (0.20, 5.35)	1.04 (0.30, 3.63)	0.994
5-day	0.84 (0.23, 3.03)	1.12 (0.14, 8.66)	1.06 (0.10, 11.0)	0.973

[a] All models are adjusted for adjusted for daily average actigraph-derived physical activity and heart rate, temperature of the same lag average, day of week, seasonal study phase (mean centered exposure), and community group (mean centered exposure), using generalized estimating equations. Daily RRs use Poisson log-link models with daily VT counts as the outcome, and hourly ORs use binomial logit-link models with hourly absence/presence of any VT as the outcome.

[b] Daytime is 06:00 to 19:00, and nighttime is 19:00 to 06:00.

[c] P-values are for heterogeneity of OR by day/night.

* $p < 0.1$, ** $p < 0.05$, # $p < 0.01$

Figure Legend

Figure 1. Associations of air pollutants and SDNN by ACE inhibitor use. $* p < 0.1$, $** p < 0.05$,

$^{\#} p < 0.01$, compared to no effect modification by ACE inhibitor use.

**Associations of SDNN with Outdoor Air Pollutants:
Effect Modification by ACE Inhibitor Medication Use**